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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/430,175	10/29/99	LESKO	S CW-304

HM22/0109

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EXAMINER	
CANELLA,K	
ART UNIT	**PAPER NUMBER**
1642	6

DATE MAILED: 01/09/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/430,175	Lesko et al
Examiner	**Group Art Unit**
Karen Canella	1642

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3 months* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-58* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-58* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ Notice to Comply

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

1. Claims 1-58 are pending and examined on the merits.

Specification

2. This application contains sequence disclosures on pg 9, first paragraph, that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is given the response period of this office action within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 34-44 and 47-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A)Claims 34, 35, 40 and 41 recite "biological probe(s)". This adjective "biological" does not further qualify "probe" since any probe directed to a cellular structure or cellular substance can be considered as a "biological probe". For purpose of examination "biological probe" will be read as a probe directed to a cellular target which is not a nucleic acid.

(B)Claims 37, 38, 39, 40 and 42 recite "molecular probe(s)". This adjective "molecular" does not further qualify "probe" since any sub-microscopic probe can be considered a "molecular

probe". For purpose of examination "molecular probe" will be read as a probe directed to a cellular target which is a nucleic acid.

(C)Claim 38 recites "DNA sequence and DNA sequences thereof". Claim 39 recites "RNA sequence and RNA sequences thereof". It is not clear how DNA/RNA "sequences" differs from DNA/RNA "sequences thereof". For purpose of examination, claim 38 will be read as "...molecular probe comprises DNA." and claim 39 will be read as "...molecular probe comprises RNA." Both claims will be read without "sequences thereof".

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

24, 27, Canceled withdrawn

6. Claims 24-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are drawn to fluorescent probes emitting light between the wavelengths of 730 nm to 814 nm, and 745 to 845 nm, with maximum emission peaks at 772 nm and 795 nm, respectively. The specification discusses only the use of the more commonly known fluorophores which can be conjugated to antibodies or intercalated in DNA, having at most a maximum emission peak of 695 nm (Cy5.5). Additional fluorophores which are useful for labeling proteins and antibodies are taught by Beavis and Pennline (Biotechniques, 1996, Vol. 21, pp. 498-503) as Sky Blue which has a maximum emission peak of 730 nm and Roederer et al (Cytometry, 1996, Vol. 24, pp. 191-197) as Cy7 tandems which have an emission maxima of 778 nm. Further, Beavis teaches that the imaging of more than six colors simultaneously is difficult due to the lack of available fluorescent probes which can be excited by available laser wavelengths and which do not give rise to significant overlap of emission spectra. Many methods have been developed

Weggone et al. A715 of the IDS

comprising complex digital imagining and data analysis of probes which have been labeled by mixtures of known fluorophores to circumvent this problem of spectral overlap (Ried et al, PNAS, 1992, Vol. 89, pp. 1388-1392; Cabib et al, USP 5,936,731; Garini et al, USP 6,066,459; Stern, USP 5,981,956). However, the instant application teaches only the selection of probes which can be distinguished from one another by the use of spectral filters. The specification does not teach a special spectral filter, a digital imaging system or data analysis system, nor does it teach specific probes which have maximum emission peaks at 772 nm and 795 nm. One of skill in the art would not be able to make or use said probe without being forced into undue experimentation to make fluorescent probes having the emission spectra as claimed.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

8. Claims 1, 6, 9-13, 14-19, 22, 23, 28-30, 33-37, 40-42, 44-46, 51, 52 and 54 rejected (6, 42, Cancelled) under 35 U.S.C. 102(b) as being anticipated by Dow et al (Cytometry, 1996, Vol. 25, pp. 1996). The instant claims are drawn to a method of characterizing single cells comprising the concurrent measurement of multiple fluorescent probes. Additional embodiments include a method of characterizing human cells, wherein the surface for cell adherence is a microscope slide, wherein the fixative is paraformaldehyde, wherein four probes are covalently liked to a fluorescent compound, wherein each fluorescent probe is selected from other probes with minimal overlapping emission spectra, wherein the fluorescent probes are selected from the group

consisting of CY3, CY5 and fluorescein isothiocyanate. Further embodiments include probes which emit light of wavelengths between 430 nm to 510 nm, 482 nm to 562 nm, between 552 nm to 582 nm, between 637 nm to 697 nm, with peak emission wavelengths of 470 nm, 522 nm, 567 nm and 667 nm, respectively. Other embodiments include antibodies which are directed toward non-nucleic acid targets. Dow et al disclose a method of characterizing human T-cells in skin biopsies taken from melanoma patients comprising the concurrent measurement of fluorescence from fluorescein isothiocyanate labeled anti-CD3 antibody (482 nm to 562 nm, 522 nm maximum), phycoerythrin labeled anti-CD4 antibody, Cy5 labeled anti-CD8 antibody (637 nm to 697 nm, 667nm maximum), Cy3 labeled anti-HLA-DR antibody (552 nm to 582 nm, 567 nm maximum) and double-stranded DNA labeled with Hoechst 3334 2(430 nm to 510 nm, 470 nm maximum). Dow et al disclose, on pg. 72, second column, last paragraph, that the labeled tissue was imaged on a microscope fitted with fluorescence filters which were chosen to minimize any overlap of detection between adjacent band fluorophores.

3, 6, 42, cancelled

9. Claims 1, 3, 5, 6, 11, 12, 13-19, 22, 23, 28-33, 37, 38, 40-42, 45 and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by Ried et al (PNAS, 1992, Vol. 89, pp. 1388-1392). The instant claims are drawn to a method of characterizing single cells comprising the concurrent measurement of multiple fluorescent probes. Additional embodiments include a method of characterizing human cells, wherein each fluorescent probe is selected from other probes with minimal overlapping emission spectra, wherein the fluorescent probes are selected from the group consisting of fluorescein isothiocyanate. Further embodiments include probes which emit light of wavelengths between 430 nm and 510 nm, 482 nm to 562 nm, 637 nm to 697 nm, and 637 nm to 697 nm, with peak emission wavelengths of about 470 nm, 522 nm, 667 nm and 667 nm, respectively. Other embodiments include probes comprising DNA. Ried et al disclose a method of characterizing chromosomes in situ comprising the concurrent detection of seven different DNA probes formed by nucleotides labeled with fluorescein isothiocyanate (emission wavelengths between 482 nm to 562 nm, maximum at 522 nm), cascade blue (emission wavelengths between 577 nm to 657 nm, maximum at 617 nm), and rhodamine, and combinations thereof. The

fluorescence was observed against a background of DAPI (emission wavelengths between 430 nm to 510 nm, maximum at 470 nm).

3, 7, 8, 57 cancelled

10. Claims 1, 3-5, 7-9, 11-13, 16, 17, 20, 21, 28, 29, 33-36, 40, 41, 43-46, 53-57 are rejected under 35 U.S.C. 102(b) as being anticipated by Gross et al (PNAS, 1995, Vol. 92, pp. 537-541). The instant claims are drawn to a method of characterizing single cells comprising the concurrent measurement of multiple fluorescent probes. Additional embodiments include a method of characterizing human cells, wherein the surface for cell adherence is a microscope slide, wherein each fluorescent probe is selected from other probes with minimal overlapping emission spectra, wherein the fluorescent probes are selected from the group consisting of fluorescein isothiocyanate and phycoerythrin. Further embodiments include probes which emit light of wavelengths between 482 nm to 562 nm and 637 nm to 697 nm, with peak emission wavelengths of 522 nm and 667 nm, respectively. Other embodiments include antibodies which are directed toward non-nucleic acid targets, and antibodies which are directed toward tissue-specific probes found on circulating cancer cells. Gross et al disclose a method of characterizing a circulating breast cancer cell in peripheral blood comprising the concurrent detection of NCL-5D3 and NCL-LP34 anti-cytokeratin antibodies to PerCP (emission wavelengths between 637 nm to 697 nm, maximum at 667 nm), CAM anti-cytokeratin antibody to PE, and AE1 anti-cytokeratin antibody to APC and fluorescein isothiocyanate conjugates (emission wavelengths between 482 nm to 562 nm, maximum at 522 nm) of anti-CD45, anti-gpIX, anti-CD61, anti-CD34 and anti-glycophorin. The anti-cytokeratin antibodies bind to tissue specific proteins associated with breast cancer.

maintain

Claim Rejections - 35 USC § 103

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor

and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

3, 7, 8, Cancelled

12. Claims 1, 2-5, 7-13, 16, 17, 20, 21, 28, 29, 33-36, 40, 41, 43-46 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gross et al (PNAS, 1995, Vol. 92, pp. 537-541) in view of what is well known in the art as exemplified by Freshney (The culture of animal Cells, 3rd edition, 1994, pp. 185-189) and Ausubel et al (Short Protocols in Molecular Biology 2nd edition, 1992, pp. 14.9-14.11). The instant claims are drawn to a method of characterizing a single cells comprising the concurrent detection of multiple fluorescent probes which is taught by Gross et al (discussed in paragraph 10, supra). Further embodiments include the isolation of the cells by density gradient centrifugation, and the fixing of said cells with a fixative solution. The isolation and fixing of cells is not taught specifically by Gross et al. The fixing of cells in preparation for in situ hybridization is taught by Ausubel et al. The isolation of cells by density gradient is taught by Freshney. It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to isolate the cells by density gradient centrifugation and fix the cells with paraformaldelhyde before using the cells in a method of characterizing single cells comprsing the concurrent detection of multiple fluorescent probes. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Fresheny on a standard protocols of isolating cells by density centrifugation and the teachings of Ausubel et al on a standard protocol of fixing cells before contacting said cells with a labeled probe.

3, 7, 8, 57, Cancelled

13. Claims 1, 2-5, 7-13, 16, 17, 20, 21, 28, 29, 33-36, 40, 41 and 43-46, 53-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gross et al and Freshney and Ausubel et al as applied to claims 1, 2-5, 7-13, 16, 17, 20, 21, 28, 29, 33-36, 40, 41, 43-46 and 54 above, and further in view of Anderson et al (Cancer Research, 1989, Vol. 49, pp. 4659-4664). The instant claims are drawn to a method of characterizing single cells comprising the concurrent detection of

multiple fluorescent probes as discussed in paragraph 12, supra. Further embodiments include a cell preparation isolated from the body by a negative selection process. Gross teaches the method as discussed in the 103(a) rejection above. Gross teaches the necessity of detecting residual contaminating tumor cells in bone marrow which has been purged ex vivo. Gross suggests (p. 537, second column, lines 5-7), but does not teach, an isolated cell preparation obtained by means of a negative selection process. Anderson teaches a method of eliminating breast cancer cells from human bone marrow, resulting in a cellular preparation of bone marrow which was obtained by a negative selection process. It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to create a cell preparation that was isolated from the body by means of a negative selection process. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Anderson et al on the method of obtaining a tumor cell-purged bone marrow sample which was generated by negative selection.

3, 7, 8, Cancelled

14. Claims 1, 2-5, 7-13, 16, 17, 20, 21, 28, 29, 33-36, 40, 41, 43-46 and 54 and 58 rejected under 35 U.S.C. 103(a) as being unpatentable over Gross et al and Freshney and ausubel et al as applied to claims 1, 2-5, 7-13, 16, 17, 20, 21, 28, 29, 33-36, 40, 41, 43-46 and 54 in paragraph 12 above, and further in view of Lebkowski et al (Transplantation, 1992, Vol. 53, pp. 1011-1019). The instant claims are drawn to a method of characterizing a single cells comprising the concurrent detection of multiple fluorescent probes which is taught by Gross et al (discussed in paragraph 9, supra). Further embodiments include a cell preparation isolated from the body by a positive selection process. Gross teaches the method as discussed in the 103(a) rejection in paragraph 11 above. Gross teaches the necessity of obtaining bone marrow which has been depleted of tumor cells for autologous transplantation. Gross teaches the detection of low-level residual tumor cells. Gross does not teach an isolated cell preparation obtained by means of a positive selection process. Lebkowski et al teach an isolated cell preparation of CD34+ cells obtained from bone marrow mononuclear cells by means of a positive selection for CD34+. It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed

invention was made to characterize a single cells preparation comprising the concurrent detection of multiple fluorescent probes, wherein the single cell preparation was obtained by means of a positive selection. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Lebkowski et al on the 99.9% depletion of tumor cells in cell populations that have undergone positive selection for CD34+ antigen.

3, 6, 7, 42, Canceled

15. Claims 1, 3, 5-7, 11, 12, 13-19, 22, 23, 28-33, 37, 38, 40-42, 45, 47, 49, 50 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fiche et al (Intl J of Cancer, 1999, Vol. 84, pp. 511-515) in view of Ried et al (PNAS, 1992, Vol. 89, pp. 1388-1392). The instant claims are drawn to a method of characterizing single cells comprising the concurrent measurement of multiple fluorescent probes. Additional embodiments include a method of characterizing human cells, wherein each fluorescent probe is selected from other probes with minimal overlapping emission spectra. Additional embodiments include molecular probes comprising DNA, said probes being used to detect copy number of the estrogen receptor and progesterone receptor. Fiche et al teach the detection of increased copy number of the c-erbB2 gene as determined by a DNA probe in a FISH assay and correlation of the increased copy number of said c-erbB2 with the detection of the estrogen receptor and the progesterone receptor as determined by immunohistochemistry. Fiche et al do not teach a FISH assay using concurrent measurement of fluorescent probes which would hybridize to c-erbB2, the estrogen receptor gene and the progesterone receptor gene. Ried et al teach a method of characterizing chromosomes in situ comprising the concurrent detection of up to seven different DNA probes (see discussion in paragraph 8, supra). It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to use a FISH assay to detect c-erbB2 gene, estrogen receptor gene and the progesterone receptor gene concurrently in a single assay. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Ried on the availability of DNA probes labeled with fluorescein isothiocyanate, rhodamine and Cascade Blue that can be visualized simultaneously without spectral overlap.

3, 6, 7, 42, Canceled

16. Claims 1, 3, 5-7, 11, 12, 13-19, 22, 23, 28-33, 37, 38, 40-42, 45, 47, 48 and 54 rejected under 35 U.S.C. 103(a) as being unpatentable over Nupponen et al (Amer. J of Pathology, 1998, Vol. 153, pp. 141-148) in view of Ried et al (PNAS, 1992, Vol. 89, pp. 1388-1392). The instant claims are drawn to a method of characterizing single cells comprising the concurrent measurement of multiple fluorescent probes. Additional embodiments include a method of characterizing human cells, wherein each fluorescent probe is selected from other probes with minimal overlapping emission spectra. Additional embodiments include molecular probes comprising DNA, said probes being used to detect copy number of an androgen receptor. Nupponen et al teach the detection of increased copy number of the c-myc gene and androgen receptor gene as determined in two separate FISH assays on prostate carcinoma cells. Nupponen et al do not teach the concurrent measurement of the c-myc gene and the androgen receptor gene copy number by FISH. Ried et al teach a method of characterizing chromosomes in situ comprising the concurrent detection of up to seven different DNA probes (see discussion in paragraph 8, supra). It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to use a FISH to detect and measure the copy number of both the c-myc gene and the androgen receptor gene concurrently in a single assay. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Ried on the convenience of using multiple fluorescent probes simultaneously when screening clinical specimens, allowing for a more definitive assessment of gene dosage with less statistical analysis.

3, 6, 7, 42, Canceled

17. Claims 1, 3, 5-7, 11, 12, 13-19, 22, 23, 28-33, 37-39, 40-42, 45, 47, 48 and 54 rejected under 35 U.S.C. 103(a) as being unpatentable over Nupponen et al and Ried et al as applied to claim 1, 3, 5-7, 11, 12, 13-19, 22, 23, 28-33, 37, 38, 40-42, 45, 47, 48 and 54 above, and further in view of what is well known in the art as exemplified by either Berenson (J of Clinical Investigation, 1995, Vol. 95, pp. 964-972) or Pajor and Bauman (Histochemistry, 1991, vol. 96, pp. 73-81). Claim 39 is drawn to the use of a molecular probe comprising RNA in a method of characterizing single cells comprising the concurrent measurement of multiple fluorescent probes.

Nupponen et al and Ried et al as teach a method of characterizing single cells comprising the concurrent measurement of multiple fluorescent probes, said fluorescent probes comprising DNA. Nupponen et al and Ried et al do not teach a method of characterizing single cells comprising the concurrent measurement of multiple fluorescent probes, said fluorescent probes comprising RNA. It is well know in the art that probes can be either DNA or RNA (Maniatis, 2nd edition, pp.10.13-10.17 and 10.27-10.37). Either Berenson or Pajor and Bauman teach the use of RNA probes in FISH assays. It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to use an RNA probe in a FISH assay. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Berenson or Pajor and Bauman on the convenience and reliability of obtaining biotinylated RNA probes for use in the FISH assay.

Conclusion

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

GEETHA P. BANSAL
PRIMARY EXAMINER

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
December 17, 2000

Application No. 09/430,175

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [x] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- [x] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [x] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [ ] 7. Other: _____

Applicant Must Provide:

- [x] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [x] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [x] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

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